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Promotion of Direct Reprogramming by Transformation-deficient Myc

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Summary

Induced pluripotent stem cells (iPSC) are generated from mouse and human fibroblasts by the introduction of three transcription factors, namely Oct3/4, Sox2, and Klf4. The protooncogene product c-Myc markedly promotes iPSC generation, but it also increases tumor formation in iPSC-derived chimera mice. We herein show that the promotion of iPSC generation by Myc is independent of its transformation property. We found that another Myc family member called L-Myc, as well as c-Myc mutants (W136E and dN2), which all possesses little transformation activity, promoted human iPSC generation more efficiently and specifically than did the wildtype c-Myc. In mice, L-Myc promoted germline transmission, but not tumor formation, in the iPSC-derived chimera mice. These data demonstrated that different functional moieties of the Myc protooncogene products are therefore involved in transformation and promotion of directed reprogramming.

¥body

Introduction

Induced pluripotent stem cells (iPSC) were first generated from mouse fibroblasts by the retroviral introduction of four transcription factors, Oct3/4, Sox2, Klf4, and c-Myc (1). Mouse iPSC are indistinguishable from embryonic stem cells (ESC) in morphology, proliferation and gene expression. Furthermore, mouse iPSC give rise to chimeric mice which are competent for germline transmission (2-4). However, we found that both the chimeras and progenies derived from mouse iPSC showed an increased incidence of tumor formations, primarily due to the reactivation of the c-Myc retrovirus (3). Subsequently, we and others succeeded in making mouse iPSC without the c-Myc retrovirus by modifying the induction protocol (5, 6). Chimeric mice derived from these c-Myc-minus iPSC did not show any increased incidence of tumor formation (6). However, the efficiency of iPSC generation is significantly lower without the c-Myc retrovirus. Indeed, c-Myc is utilized in most of the reported methods to generate iPSC without viral integrations (7-15). Therefore, c-Myc functions as a double-edged sword in that it promotes both iPSC generation and tumorigenicity.

In addition to the overexpression of c-Myc, we and others have shown the suppression of the tumor suppressor gene p53 to also significantly enhance iPSC generation (16-19).

The downstream targets of p53, including p21 and Arf/Ink4, are also involved in the suppression of iPSC generation. The fact that the two most common pathways associated with human cancers, namely the activation of c-Myc and the suppression of p53, both substantially enhance iPS generation raise the possibility that the molecular mechanisms underlying iPSC generation and tumorigenicity thus largely overlap.

The Myc protooncogene family consists of three members; c-Myc, N-Myc, and L-Myc (20-23). All three members dimerize with Max and binding to DNA (24). N-Myc is similar to c-Myc regarding its length, domain structures, and frequent association with human cancers (25). In contrast, the L-Myc protein demonstrates shorter amino acid sequences than the other two members in the N-terminal region, while also possessing a significantly lower transformation activity in cultured cells (21, 26-29). Consistent with this property, only a small number of human cancers have been associated with the aberrant expression of L-Myc. In this study, we analyzed the effect of L-Myc in the promotion of iPSC generation. Despite its weak transformation activity, we found L-Myc to have a stronger and more specific activity in promoting iPSC generation. We also found that the mutations which significantly deteriorate the transformation activity of c-Myc more effectively and specifically promoted human iPSC generation. These results demonstrated that the promotion of nuclear-reprogramming and transformation

activity are independent properties of the Myc family proteins.

Results

In order to compare the effects of L-Myc, N-Myc, and c-Myc on human iPSC generation, we retrovirally transduced human adult dermal fibroblasts with Oct3/4, Sox2, and Klf4, with or without the Myc family members. Three weeks thereafter, we counted the numbers of both iPSC colonies, which showed an ES cell-like morphology with a flat and round shape and characterized by a distinct edge, as well as non-iPSC colonies which were granules and demonstrated an irregular edge. We thus found L-Myc to have a significantly more potent ability to increase the number of iPSC colonies than c-Myc (Figure 1A). N-Myc also tended to increase the iPSC colonies more effectively than did c-Myc, albeit the difference was not statistically significant. We also found that c-Myc and N-Myc markedly increased the formation of non-iPSC colonies, whereas L-Myc did not show any such effect. As a result, the proportion of iPSC colonies to total colonies is significantly higher with L-Myc than with c-Myc or N-Myc (Figure 1B).

Human iPSC generated with L-Myc showed a morphology similar to that of hESC (Figure 1C). They are positive for various pluripotent markers, such as Tra-1-60, Tra-1-81, SSEA-3, and Oct3/4 (Figure S1A). They differentiated into various tissues of three germ layers, including neural tissues, gut-like epithelial cells, cartilage, and

adipose tissue, in teratomas (Figure S1B) and in embryoid bodies (Figure S1C). They have normal karyotypes (Figure S1D). These results demonstrated that L-Myc more specifically and effectively promotes human iPSC generation than does c-Myc.

We next compared the three Myc members in mouse iPSC generation. Mouse embryonic fibroblasts (MEF), which have a GFP-reporter driven by the regulatory regions of the mouse *Nanog* gene, were retrovirally transduced with Oct3/4, Sox2, and Klf4, with or without each of the Myc family members. Three weeks thereafter, we counted the numbers of GFP-positive and GFP-negative colonies. GFP-positive colonies represent fully reprogrammed iPSC, whereas GFP-negative colonies represent partially reprogrammed cells or transformed cells. As has been reported previously (6), all the three Myc proteins enhanced generation of GFP-positive colonies (Figure 2A). The effect of c-Myc is stronger than the other two members, but it increased the number of GFP-negative colonies more profoundly than the GFP-positive ones, thus resulting in a significant decrease in the proportion of GFP-positive colonies to total colonies (Figure 2B). In contrast, L-Myc preferentially increased GFP-positive colonies, while the proportion of GFP-positive colonies to the total colonies remained high. These results demonstrated that L-Myc specifically enhances the generation of fully reprogrammed mouse iPSC.

Mouse iPS cells generated with L-Myc showed an ES-like morphology (Figure S2A) and express pluripotent-associated genes, such as *Nanog*, *Rex1*, *ECAT1*, and *ESG1* (Figure S2B). The expression of retroviral transgenes was effectively silenced. When transplanted subcutaneously into nude nice, they formed teratomas containing various tissues, such as neural tissues, gut-like epithelial tissues and striated muscles (Figure S2C). Furthermore, when injected into blastocysts, L-Myc iPS cells were capable of producing high percentage chimeras, which were competent for germline transmission. Of note, we found that both c-Myc and L-Myc promoted germline transmission from chimeras in comparison to iPS cells generated without the Myc transgenes (Figure 3A). Therefore, iPSC generated with L-Myc are of a comparable quality to ES cells.

We have previously shown that iPSC generated with the c-Myc retrovirus resulted in a markedly increased tumor formation and mortality in chimeras and progeny mice (3, 30). In contrast, iPSC generated without the c-Myc transgene did not show any such adverse effects in mice (6). In this study, we observed chimeras derived from L-Myc iPSC clones up to two years. In great contrast to c-Myc, the L-Myc retrovirus did not result in any marked increase in either tumorigenicity or mortality (Figure 3B). When compared to chimeric mice derived from Myc-minus iPS cells, L-Myc iPS cells did show a slightly higher mortality, but not tumorigenicity, in mice after one

year from birth. Causes of death in these mice are yet to be determined. This result is consistent with the weak transformation activity of L-Myc.

We also examined whether L-Myc was capable of decreasing the number of factors required for iPSC generation. We found that with the addition of L-Myc, iPSC can be generated without Sox2. When 1 x 10^5 Nanog-GFP reporter MEFs were infected with Oct3/4, Klf4, and L-Myc, we obtained 16 GFP-positive colonies. In contrast, we did not obtain any GFP-positive colonies without the L-Myc transgene. We picked up all of these colonies and were able to establish iPSC lines from 15 clones. These Sox2-minus iPSC showed an ES-like morphology (Figure S3A) and express ES cell markers such as *Nanog*, *Rex1*, and *ECAT1* (Figure S3B). We confirmed the absence of the Sox2 transgene by genomic PCR (Figure S3C). These cells can differentiate into cells of three germ layers in teratomas (Figure S3D) and in embryoid bodies (Figure S3E). Sox2-minus L-Myc iPS cells were capable of producing chimeras, which were competent for germline transmission (Figure S3F).

We next examined the correlation between the ability to promote iPSC generation and the transformation activity of the Myc proteins. We constructed the W136E c-Myc mutant which has been reported to lack transformation activity, but it still binds to Max and DNA (26, 31). We also generated a mutant of c-Myc that does not

bind to Miz-1 (V394D) (32) and other mutants of c-Myc and L-Myc that do not bind to Max (c-Myc L420P and L-Myc L351P) (33). We confirmed that the wildtype L-Myc, the W136E c-Myc mutant, the L420P c-Myc mutant, and the L351P L-Myc mutant showed little transformation activity in NIH3T3 cells (Figure 4A). In contrast, the wildtype c-Myc and the V394D c-Myc mutant induced transformation is characterized by a high refractivity and a spindle-like shape. We then introduced either the wildtype or the mutant c-Myc into adult human dermal fibroblasts together with Oct3/4, Sox2, and Klf4 to generate iPSC colonies. We found the W136E c-Myc mutant to function in a similar manner to that of L-Myc; it increases the number of iPSC colonies more effectively than the wildtype c-Myc (Figure 4B). The proportion of iPSC colonies to total colonies was also higher with the W136E mutant that with the wildtype c-Myc (Figure S4A). The V394D c-Myc mutant was comparable to the wildtype c-Myc, thus indicating that the binding to Miz-1 does not play positive nor negative roles in the promotion of iPSC generation. The L420P c-Myc or L351P L-Myc mutant did not promote iPSC generation, thereby demonstrating the essential role of Max binding. Similar results were obtained in mice (Figure S4C and D); the W136E c-Myc mutant, like L-Myc, specifically promoted mouse iPSC generation, whereas the V394D c-Myc mutant, like the wildtype c-Myc, promoted both iPSC and non-iPSC generation.

We also constructed c-Myc mutants that have a shorter N-terminus; dN1 and dN2. The c-Myc protein is ~22 amino acids longer than L-Myc in the N-terminus. These extra amino acids were deleted in the dN2 mutant, whereas only 14 amino acids were deleted in the dN1 mutant. We found that the dN2 mutant showed little transformation activity in NIH3T3 cells, whereas the dN1 mutant was comparable to the wildtype c-Myc (Figure 4C). The dN2 mutant showed a similar property with the wildtype L-Myc and the W136E c-Myc mutant during iPSC generation in both human (Figure 4D and S4B) and mouse (Figure S4E and F). In contrast, the dN1 mutant was comparable to the wildtype c-Myc. These data, taken together, showed that the promotion of iPSC generation by Myc therefore is not parallel to its transformation activity.

To elucidate the molecular mechanisms underlying the different effects of c-Myc and L-Myc during iPSC generation, we performed DNA microarray analyses. We expressed either c-Myc (wildtype, W136E, V394D, or L420P) or L-Myc (wildtype or L351P) in human adult dermal fibroblasts by retroviruses. Two days after transduction, we isolated total RNA for microarray analyses. We categorized genes that either increased or decreased more than two-fold by Myc into four groups as follows: group A, increased > 2-fold by wildtype c-Myc and the V394D c-Myc mutant compared to mock-transduced control (Mock) and the L420P c-Myc mutant; group B, decreased >

2-fold by wildtype c-Myc and the V394D c-Myc mutant compared to Mock and the L420P c-Myc mutant; group C, increased > 2-fold by wildtype L-Myc and the W136E c-Myc mutant compared to Mock and the corresponding Max-biding deficient mutant; and group D, decreased > 2-fold by wildtype L-Myc and the W136E c-Myc mutant compared to Mock and the Max-biding deficient mutant. Groups A and B represent the genes regulated by Myc proteins which promote both iPSC generation and transformation. Groups C and D represent genes regulated by Myc proteins which specifically promote iPSC generation, but not transformation.

We found that c-Myc and L-Myc regulate both common (subgroups AC and BD in Figure 5A) and unique target genes (subgroups A, C, B, and D in Figure 5A) Genes in each subgroup are shown in **Supplementary Table 1**. Subgroups A and AC are enriched with genes that are highly expressed in human ES cells as well as cancer cells, such as bladder tumors and nasopharyngeal carcinoma (NPC) (Figure 5B and C). The increased expression of these genes may be associated with the transformation activity of Myc. In contrast, subgroups BD and D are enriched with genes which are highly expressed in fibroblasts, but not in ESC or iPSC. This result suggests that the promotion of iPSC generation by Myc might be associated with the suppression of fibroblast-specific genes and that L-Myc is more potent than c-Myc in this specific gene

regulation.

Discussion

In the current study, we found that L-Myc shows the strongest and the most specific activity in promoting human iPSC generation among the three Myc family proteins, c-Myc, N-Myc, and L-Myc. This was surprising since L-Myc has been shown to have the weakest transformation activity among the three proteins (21, 25, 26, 28). We also found that the mutations which deteriorate the transformation activity of c-Myc specifically promote iPSC generation. Our findings demonstrated that iPSC generation and transformation utilize different functional moieties of the Myc protooncogene products.

DNA microarray analyses suggested that L-Myc and the transformation-deficient W136E c-Myc mutant have the different target genes from the wildtype c-Myc. When overexpressed in human dermal fibroblasts, L-Myc and the W136E c-Myc mutant suppressed many genes that were highly expressed in fibroblasts in comparison to iPSC or ESC. In contrast, only a small number of genes were selectively activated by L-Myc and the W136E c-Myc. We therefore postulate that the primary role of these Myc proteins in promoting iPSC generation might be to suppress differentiation-associated genes. This finding is consistent with a previous report about c-Myc (34) and we also found both L-Myc and the W136E c-Myc mutant to be more

potent than the wildtype c-Myc .

DNA microarray analyses also found that the wildtype c-Myc protein activates many genes that are enriched not only in ESC and iPSC, but also in cancer cells. These gene products might be associated with cell proliferation, immortality and cell metabolisms. Approximately a half of these are specifically activated by the wildtype c-Myc, but not by L-Myc or the W136E c-Myc mutant. These genes are might be responsible, at least in part, for the transformation activity of c-Myc.

We found that the effects of L-Myc and the transformation-deficient mutants of c-Myc in enhancing iPSC generation were more potent in human than in mouse. Reasons for this discrepancy are yet to be determined. It may suggest that molecular mechanisms underlying iPSC generation might be similar, but not identical, between human and mouse.

Since its first demonstration in 2006, iPSC generation has been associated with transformation and tumorigenicity (1). First of all, all the four factors required for iPSC generation have been associated in human cancers. The most obvious example is c-Myc, one of the first protooncogene identified in human cancers (35). The aberrant expression of c-Myc is found in more than fifty percent of human cancers. Klf4 plays a unique role in cancers in that it functions as both a protooncogene and a tumor suppressor gene (36).

Klf4 promotes cellular transformation by suppressing p53, but it also enhances the activity of p21, and therefore it may function as a tumor suppressor depending on the cellular context (37). The aberrant expression of Oct3/4 and Sox2 has also been found in some germ cell tumors and other tumors (38-42).

The association of iPSC generation and transformation has also become evident by the increased incidence of tumor formation observed in chimeric mice derived from iPSC (3, 30). More than fifty percent of chimeras derived from MEF-derived four factors-induced iPSC developed tumors within one year after birth. In these tumors, a reactivation of the c-Myc retrovirus was detected. In contrast, chimeras derived from iPSC generated without the c-Myc retrovirus did not show any such increased incidence of tumorigenicity (6). Therefore, c-Myc seems to play a major role in the observed tumorigenicity in iPSC-derived mice.

More recently, multiple groups have independently shown the suppression of the tumor-suppressor gene p53 to markedly enhance iPSC generation (16-19). The loss of the p53 functions, like the aberrant expression of c-Myc, has been associated with many human tumors (43-47). All of these findings, taken together, indicate that iPSC generation and cellular transformation have many molecular mechanisms and pathways in common, and therefore increasing the efficacy of iPSC generation can be

achieved at the expense of increased tumor formation.

In contrast to these predictions, our data showed that iPSC generation and transformation by Myc are largely independent. The former was mainly attributable to the suppression of genes that are highly expressed in fibroblasts, but not in iPSC or ESC. In contrast, transformation is attributable to the activation of genes that are enriched in highly proliferative cells, including cancer cells, iPSC and ESC. Although methods of iPSC generation which do not result in permanent integration of transgenes have been reported (7-15), even the transient expression of the c-Myc transgene may cause detrimental effects on the resulting iPSC. Therefore, the usage of L-Myc or transformation-deficient mutants of c-Myc should be beneficial for the future clinical applications of iPSC technologies.

Materials and Methods

Plasmid constructions

pMXs-based retroviral vectors for the mouse Myc family genes have been described previously (6). The coding regions of human L-Myc and N-Myc were amplified by RT-PCR with primers listed in **Supplementary Table 2**. N-terminus deleted c-Myc mutants (cdN1; 14-439 aa, cdN2; 42-439 aa) were amplified by the PCR primers listed in **Supplementary Table 3**. These PCR products were subcloned into pENTR-D-TOPO (Invitrogen), and recombined with pMXs-gw by the LR reaction (Invitrogen). For the construction of Myc point mutants, site-directed mutagenesis was performed using PrimeSTAR HS DNA Polymerase (Takara, Japan) with primers listed in **Supplementary Table 4**, according to the manufacturer's instructions.

Generation of iPSC

The induction of mouse iPSC was performed as previously described (1, 3, 6) with some modifications. Briefly, mouse embryonic fibroblasts (MEF) which contained the Nanog-GFP-IRES-Puro^r reporter were seeded at 1.0 x 10^5 cells/well in 6-well plates. Next day, the cells were infected with retorvirsuses containing three or four factors (day 0). On day 3, the cells were replated onto mitomycin C-treated SNL feeder cells (48).

The transduced cells were cultivated with ES medium containing LIF (49). Selection with puromycin (1.5 μg/ml) was started at day 21. Twenty-five to 30 days after transduction, the number of colonies was manually counted under a phase-contrast microscope and recorded. Some colonies were then selected for expansion. The induction of human iPSC was performed as described previously (6, 50). Adult human dermal fibroblasts (aHDF) from the facial dermis of 36-year-old Caucasian female were purchased from Cell Applications, Inc.

RNA isolation and reverse transcription

The purifications of total RNA and RT-PCR were performed as previously described (1, 3, 6, 50). The expression of L-Myc was detected with a primer set that is listed in **Supplementary Table 5**.

Transformation assay in NIH3T3 cells

NIH3T3 cells were plated at 2.5 x 10^4 cells/well in 24-well plates. Next day, the cells were infected with Myc-wild type or mutants. Two days after infection, the transfomation activity was determined based on the morphological changes.

DNA microarray analyses

A DNA microarray analysis was performed as previously described (50). HDF were retrovirally infected with wildtype or mutant Myc. Forty-eight hours after infection, total RNA was extracted from the cells and used for microarray experiments (GSE22654). Data were analyzed by the GeneSpring GX 11 software package (Agilent). The genes activated or suppressed by Myc proteins were selected and categorized as described in the **Results** section. According to the expression levels of these selected genes, hierarchical clustering of the log2 expression ratios was performed for five cancer cells, two normal cells (HDF and lung fibroblasts), human iPS cells (average of three clones; 201B2, 201B7, and 253G1), and human ES cells (average of four clones; H1, H9, KhES1, and KhES3). The microarray data of cancer cells and lung fibroblasts were obtained from GEO DataSets (adenocarcinomas; GSE13213, bladder cancer; GSE19716, glioblastoma; GSE10878, nasopharyngeal carcinoma; GSE15191, stromal tumor; GSE17018, lung fibroblasts; GSE15359).

Statistical analyses

Data are shown in averages ± standard deviations. All statistical analyses were performed with One-Way Repeated-Measures ANOVA and Bonferroni Post Hoc test,

using KaleidaGraph 4 (HULINKS, Japan).

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Figure Legends

Figure 1 Promotion of human iPSC generation by L-Myc

(A) The number of human iPSC colonies from HDFs transduced with or without the indicated Myc family genes. (n=4, **P<0.01 versus wo Myc or c-Myc).

(B) The effect of Myc on the percentage of human iPS cell colonies per all colonies (n=4, **P<0.01 versus c-Myc or N-Myc).

(C) Morphology of L-Myc hiPSC. Scale bar, 200 μm.

Figure 2 Generation of mouse iPSC with L-Myc

(A) Generation of mouse iPSC with or without the indicated Myc family genes from MEF containing the Nanog-GFP reporter. The raw data from five independent experiments are shown (Exp. No. 1-5). Each red line shows the average of five experiments in the indicated condition.

(B) Effect of the Myc family genes on the percentage of GFP-positive colonies per all colonies (n=5, *P<0.05, **P<0.01).

Figure 3 Chimeric Mice derived from L-Myc iPSC

(A) Frequency of germline transmission of mouse iPSC clones established without Myc

or with either c-Myc or L-Myc. The white columns show how many iPSC clones gave rise to germline transmission, whereas the grey columns show how many clones were tested. Also shown are the percentages of germline-competent iPSC clones to all clones tested.

(B) The cumulative overall mortality (upper panel) and morality with microscopically obvious tumors (lower panel) in the chimera mice derived from iPSC with c-Myc or L-Myc. Numbers in parentheses show the total number of animals tested in each group.

Figure 4 Promotion of iPSC generation by transformation-deficient Myc mutants

(A) Transformation activity of wildtype and mutants Myc in NIH3T3 cells. Scale bar, 100 μm.

(B) Generation of human iPSC with Myc mutants. The numbers of hiPSC colonies are shown (n=9, *P<0.05 versus wildtype c-Myc).

(C) Transformation activity of N-terminus deleted c-Myc mutants in NIH3T3 cells. Scale bar, 100 μm.

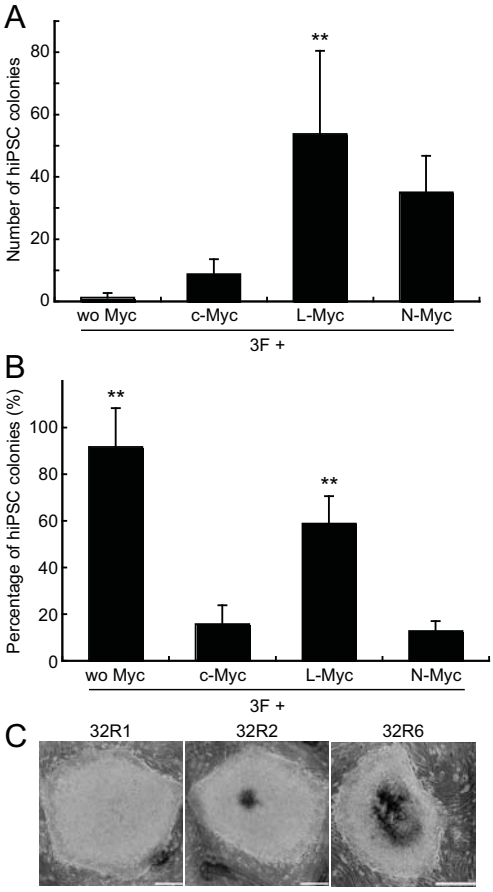
(D) Generation of human iPS cells by N-terminus deleted c-Myc mutants. The numbers of hiPSC colonies are shown (n=3, *P<0.05 versus wildtype or dN1 c-Myc, **P<0.01 versus wo Myc).

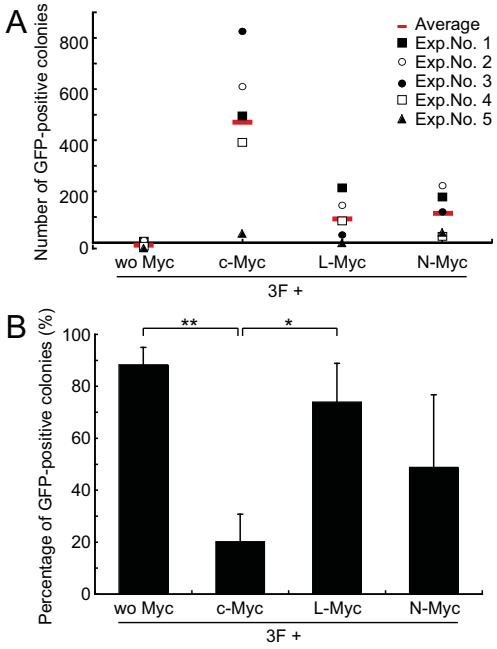
Figure 5 Genes regulated by Myc proteins

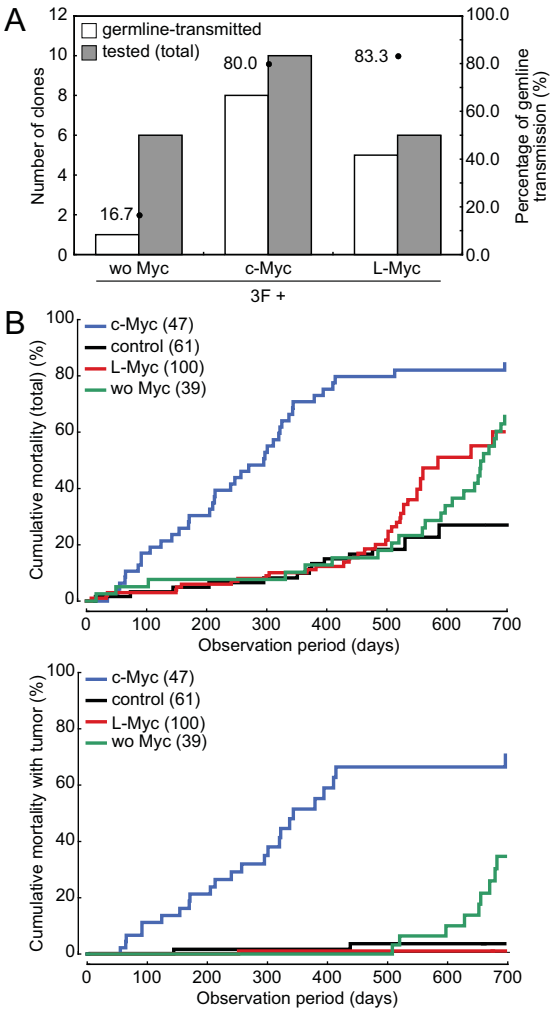
(A) Subgroups of the genes regulated by Myc proteins. Venn diagrams were constructed from the group A, B, C, and D. The numbers of the genes in each list are shown. These genes are listed in **Supplementary Table 1.**

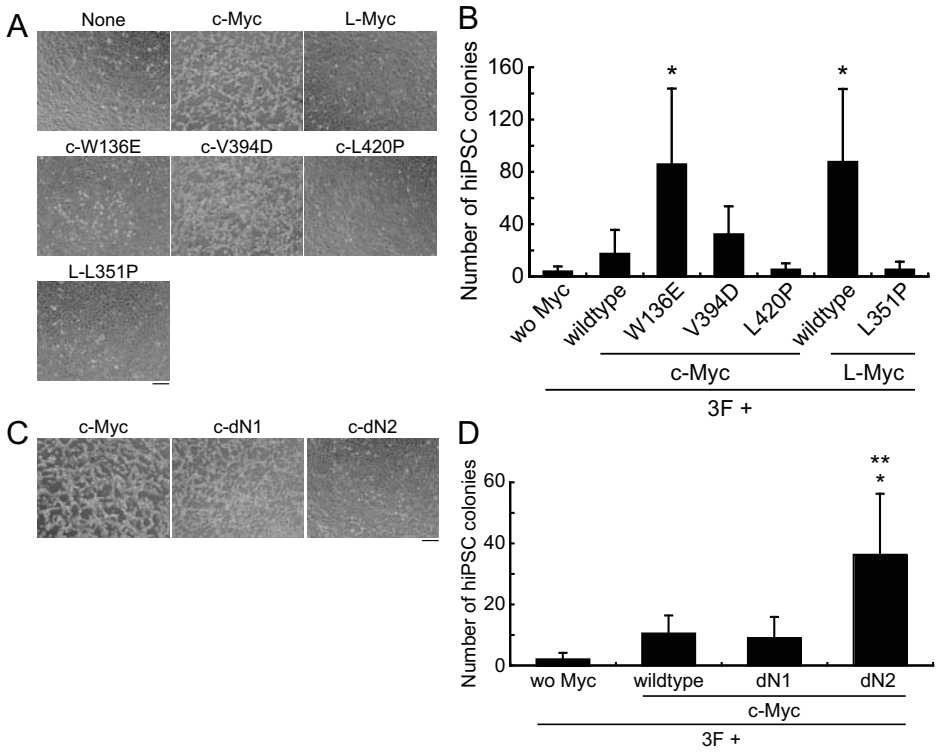
(B) Regulation of aHDF- or ES cell- enriched genes by Myc. The numbers of genes are shown whose expression is >5 fold higher or lower in hESC (H9) than in adult human dermal fibroblasts (aHDF) in each subgroup.

(C) Comparison of gene expression in cancer cells, normal fibroblasts, iPSC and ESC. The expression levels of the genes in each subgroup in five cancer cells, two normal fibroblasts, human iPSC (average of three clones; 201B2, 201B7, and 253G1), and human ESC are shown (average of four clones; H1, H9, KhES1, and KhES3). Adeno, adenocarcinomas; Bladder, bladder cancer; GBM, glioblastoma; NPC, nasopharyngeal carcinoma; Stromal, stromal tumor; and Lung fibro, normal lung fibroblasts.









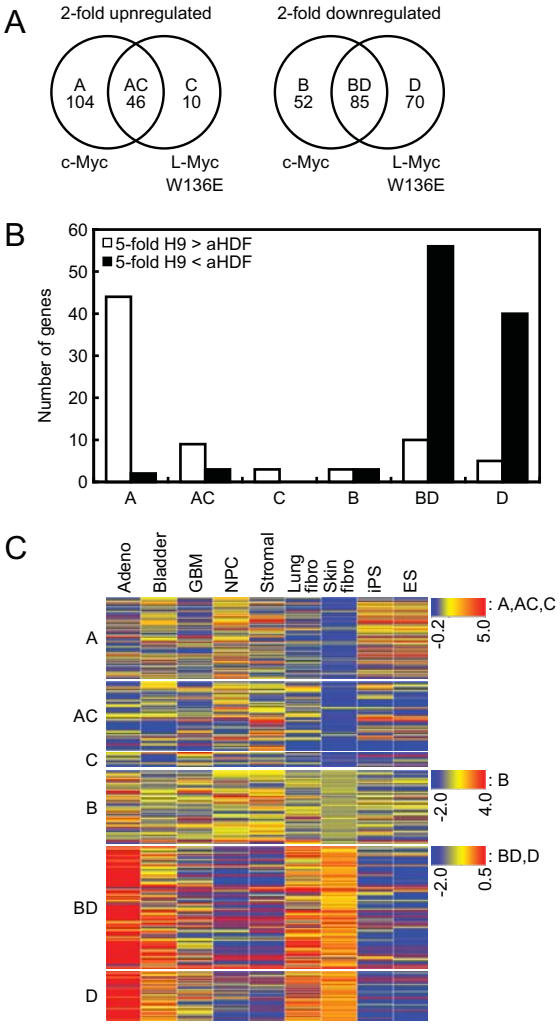


Figure S1 Characterization of human L-Myc iPSC in vitro.

(A) Immunostaining of human ES marker genes in L-Myc hiPSC. Scale bar, 500 μm.

(B) Various tissues observed in teratomas from L-Myc hiPSC. Scale bars, 100 μm.

(C) Human L-Myc iPS cells differentiated into several lineages of somatic cells in vitro through embryonic body formation. Scale bar, 100 μm.

(D) Karyotype analysis. A normal karyotype was maintained after prolonged passages (up to passage 55). Fifty metaphases were analyzed for each clone.

Figure S2 Characterization of mouse L-Myc iPSC in vitro.

(A) Morphology of mouse iPSC established with L-Myc. The phase contrast (PH) and fluorescent images of six independent clones are shown. Scale bar, 500 μm.

(B) RT-PCR analyses of ES marker genes and retroviral transgenes (Tg). *Nanog* and other ES marker genes expressed in iPSC with L-myc. The clones 142C2 or 142E9 were partially reprogrammed cells which maintain highly transgene expression of the three factors (Oct3/4, Sox2, and Klf4), plus either c-Myc (142C2) or L-Myc (142E9).

(C) Hematoxylin and eosin staining of teratomas derived from mouse L-Myc iPSC. Scale bar, 100 μm.

Figure S3 Generation of mouse iPSC without Sox2

(A) Fluorescent (upper panel) and phase contrast (lower panel) images of mouse iPSC clones generated with Oct3/4, Klf4, and L-Myc. Scale bar, 500 μm.

(B) RT-PCR analyses for the expression of ES marker genes and retroviral transgenes.

(C) Genomic-PCR analyses for the detection of integrated transgenes.

(D) Teratomas derived from Sox2-minus iPSC clones. Scale bar, 100 μm.

(E) Various tissues observed in embryoid bodies from Sox2-minus iPSC clones. Scale bar, 100 μm.

(F) Germline transmission of a Sox2-minus iPSC clone.

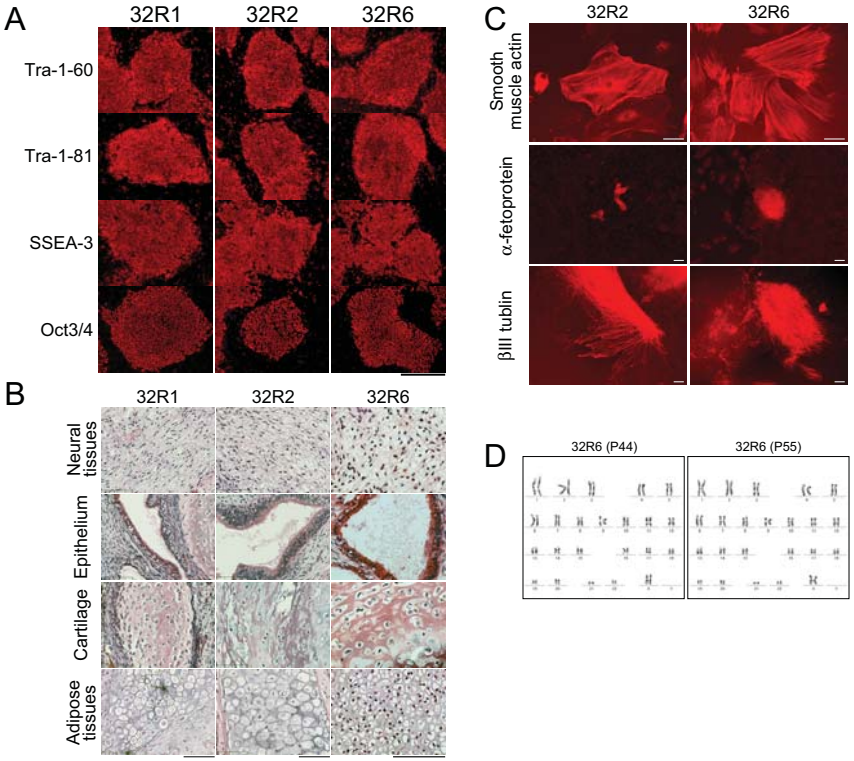
Figure S4 Generation of iPS cells by Myc mutants.

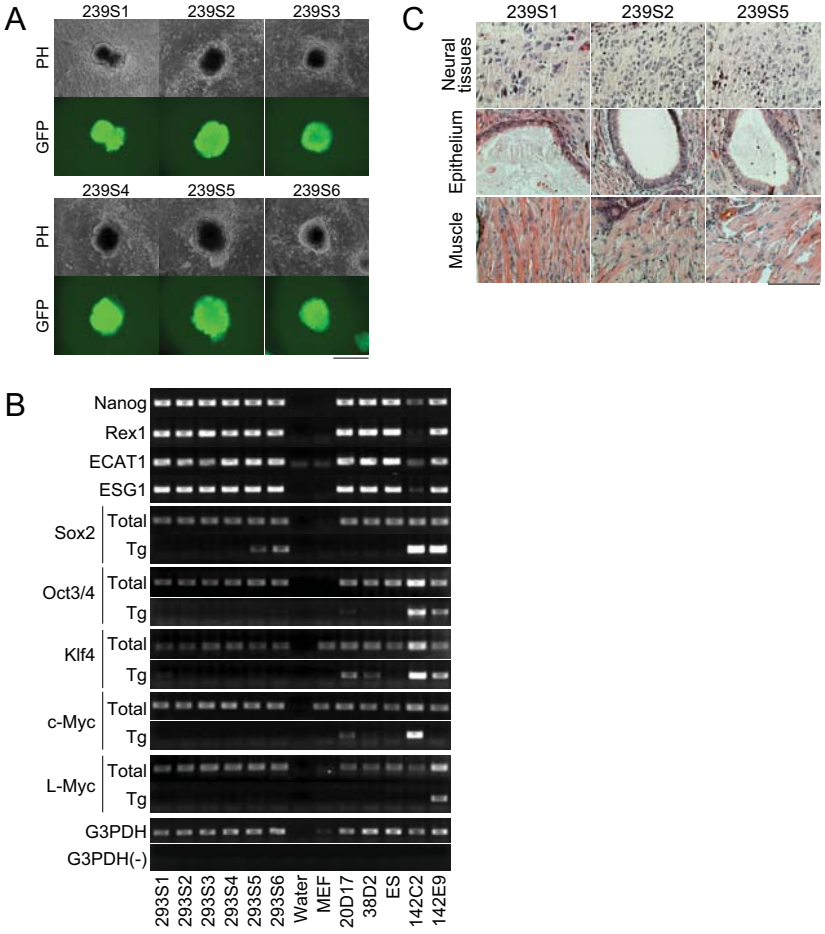
(A) Generation of human iPSC with Myc mutants. The percentages of hiPSC colonies per all colonies are shown (n=9, *P<0.05 versus wildtype c-Myc, **P<0.01 versus wildtype c-Myc).

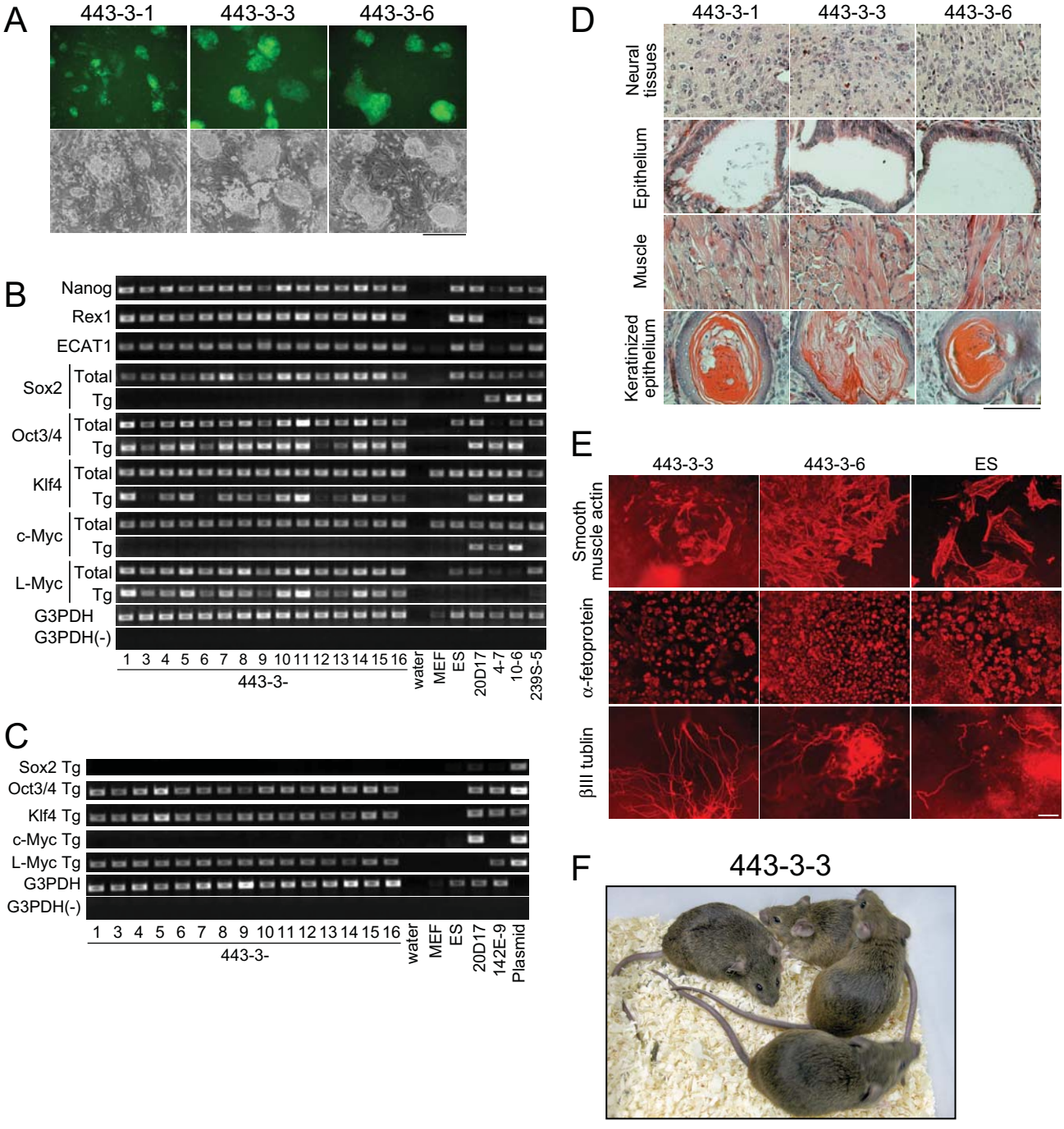
(B) Generation of human iPS cells by N-terminus deleted c-Myc mutants. The percentages of hiPSC colonies per total colonies are shown (n=3, **P<0.01 versus wildtype or dN1 c-Myc).

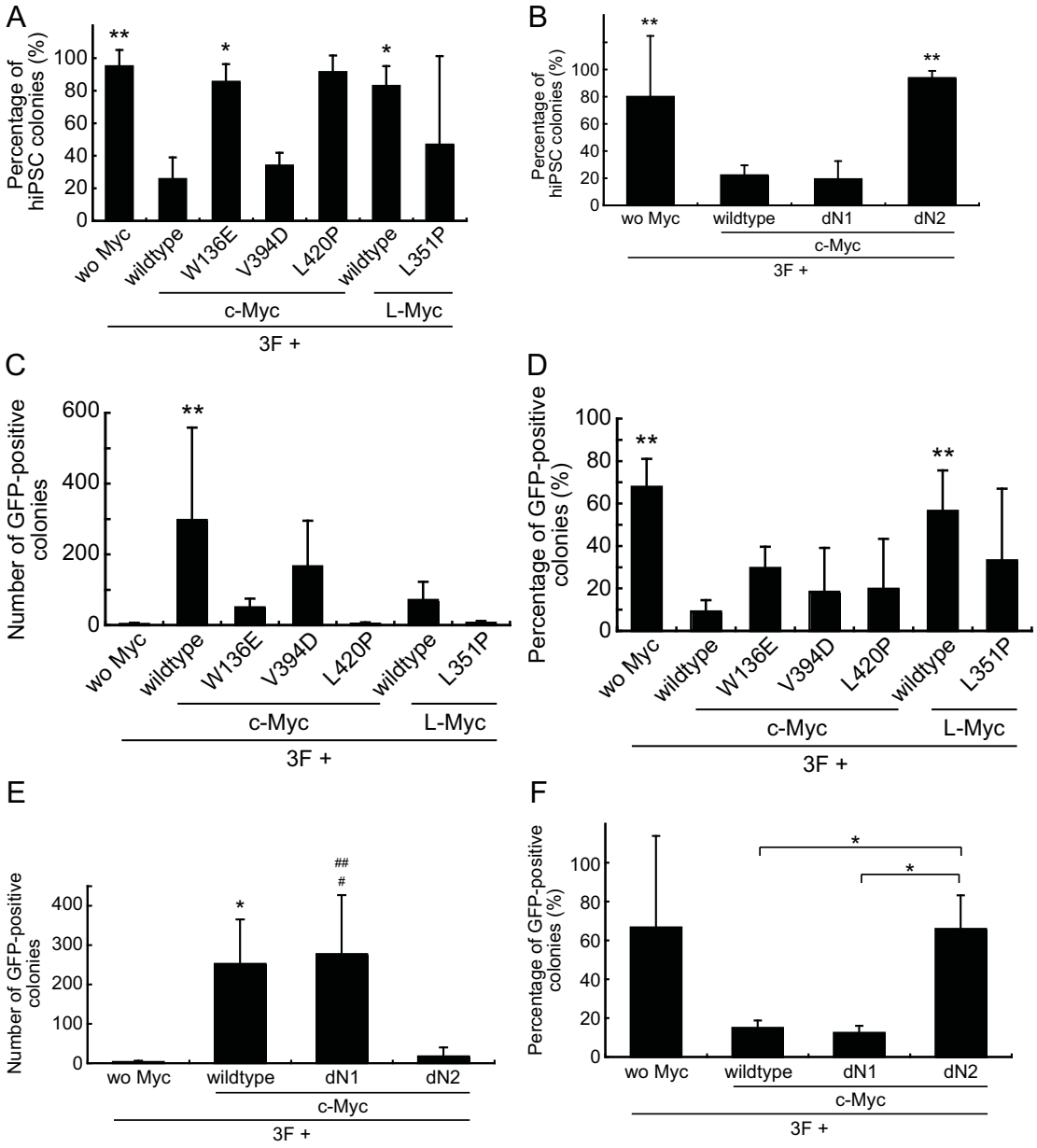
Generation of mouse iPSC with Myc mutants. The numbers of GFP-positive (C) and percentages of GFP-positive (D) colonies are shown (n=4, **P<0.01 versus all other conditions except for V394D c-Myc (C), **P<0.01 versus wildtype c-Myc (D)).

Generation of mouse iPSC with N-terminus deleted c-Myc mutants. The numbers of GFP-positive (E) and percentages of GFP-positive (F) colonies are shown (n=4, *P<0.05 versus wo Myc or dN2 c-Myc (E), #P<0.05 versus dN2 c-Myc, ##P<0.01 versus wo Myc).









Group A

GeneSymbol	Description
A_23_P88554	
A_24_P238819	
A_24_P272515	
A_24_P324538	
A_24_P332911	
A_24_P375550	
A_24_P418786	
A_24_P565496	
A_24_P850336	
A_32_P82179	
A_32_P89049	
AB062488	Homo sapiens OK/SW-cl.92 mRNA, complete cds. [AB062488]
ACTL8	Homo sapiens actin-like 8 (ACTL8), mRNA [NM_030812]
ADAM11	Homo sapiens ADAM metallopeptidase domain 11 (ADAM11), mRNA [NM_002390]
AF086124	Homo sapiens full length insert cDNA clone ZA79C08. [AF086124]
AGPAT5	Homo sapiens 1-acylglycerol-3-phosphate O-acyltransferase 5 (lysophosphatidic acid acyltransferase, epsilon) (AGPAT5), mRNA [NM_018361]
AI278811	AI278811 qo50a11.x1 NCI_CGAP_Co8 Homo sapiens cDNA clone IMAGE:1911932 3' similar to gb:K02276 MYC PROTO-ONCOGENE PROTEIN (HUMAN);, mRNA sequence [AI278811]
AK021715	Homo sapiens cDNA FLJ11653 fis, clone HEMBA1004538. [AK021715]
AK022337	Homo sapiens cDNA FLJ12275 fis, clone MAMMA1001686. [AK022337]
ALS2CR13	Homo sapiens amyotrophic lateral sclerosis 2 (juvenile) chromosome region, candidate 13 (ALS2CR13), mRNA [NM_173511]
ANP32C	Homo sapiens acidic (leucine-rich) nuclear phosphoprotein 32 family, member C (ANP32C), mRNA [NM_012403]
BAX	Homo sapiens BCL2-associated X protein (BAX), transcript variant epsilon, mRNA [NM_138764]
BC029473	Homo sapiens cDNA clone IMAGE:4723680, **** WARNING: chimeric clone ****. [BC029473]
BC041996	Homo sapiens cDNA clone IMAGE:5310797. [BC041996]
BU567141	AGENCOURT_10393620 NIH_MGC_141 Homo sapiens cDNA clone IMAGE:6606733 5', mRNA sequence [BU567141]
C10orf95	Homo sapiens chromosome 10 open reading frame 95 (C10orf95), mRNA [NM_024886]
C20orf42	Homo sapiens chromosome 20 open reading frame 42 (C20orf42), mRNA [NM_017671]
C7orf40	Homo sapiens cDNA FLJ38860 fis, clone MESAN2011977. [AK096179]
CCDC47	Homo sapiens coiled-coil domain containing 47 (CCDC47), mRNA [NM_020198]
CCDC78	Homo sapiens coiled-coil domain containing 78 (CCDC78), transcript variant 2, mRNA [NM_173476]
CD3EAP	Homo sapiens CD3e molecule, epsilon associated protein (CD3EAP), mRNA [NM_012099]
CD79B	Homo sapiens CD79b molecule, immunoglobulin-associated beta (CD79B), transcript variant 1, mRNA [NM_000626]
CDC42BPG	Serine/threonine-protein kinase MRCK gamma (EC 2.7.11.1) (CDC42- binding protein kinase gamma) (Myotonic dystrophy kinase-related CDC42-binding kinase gamma) (Myotonic dystrophy protein kinase-like alpha) (MRCK gamma) (DMPK-like gamma)....
CDK5R1	Homo sapiens cyclin-dependent kinase 5, regulatory subunit 1 (p35) (CDK5R1), mRNA [NM_003885]
CYFIP2	Homo sapiens cytoplasmic FMR1 interacting protein 2 (CYFIP2), transcript variant 2, mRNA [NM_001037332]
CYP2J2	Homo sapiens cytochrome P450, family 2, subfamily J, polypeptide 2 (CYP2J2), mRNA [NM_000775]
DHODH	Homo sapiens dihydroorotate dehydrogenase (DHODH), nuclear gene encoding mitochondrial protein, transcript variant 1, mRNA [NM_001361]
DLEU1	Homo sapiens deleted in lymphocytic leukemia, 1 (DLEU1) on chromosome 13 [NR_002605]
DLL3	Homo sapiens delta-like 3 (Drosophila) (DLL3), transcript variant 2, mRNA [NM_203486]
DQ786230	Homo sapiens clone HLS_IMAGE_1706664 mRNA sequence. [DQ786230]
DRD5	Homo sapiens dopamine receptor D5 (DRD5), mRNA [NM_000798]
DUSP2	Homo sapiens dual specificity phosphatase 2 (DUSP2), mRNA [NM_004418]
ENST00000379864	OTTHUMP00000018257. [Source:Uniprot/SPTREMBL;Acc:Q9H1T5] [ENST00000379864]
ERF	Homo sapiens Ets2 repressor factor (ERF), mRNA [NM_006494]
EXOC6	Homo sapiens exocyst complex component 6 (EXOC6), transcript variant 2, mRNA [NM_001013848]
EXOSC5	Homo sapiens exosome component 5 (EXOSC5), mRNA [NM_020158]
FABP5	Homo sapiens fatty acid binding protein 5 (psoriasis-associated) (FABP5), mRNA [NM_001444]
FAM60A	Homo sapiens family with sequence similarity 60, member A (FAM60A), mRNA [NM_021238]
FAM81A	Homo sapiens family with sequence similarity 81, member A (FAM81A), mRNA [NM_152450]
FKBP4	Homo sapiens FK506 binding protein 4, 59kDa (FKBP4), mRNA [NM_002014]
FLJ38359	Homo sapiens cDNA FLJ38359 fis, clone FEBRA2000321. [AK095678]
GPSM1	Homo sapiens G-protein signalling modulator 1 (AGS3-like, C. elegans), mRNA (cDNA clone MGC:16636 IMAGE:4121647), complete cds. [BC009979]
HSPA4L	Homo sapiens heat shock 70kDa protein 4-like (HSPA4L), mRNA [NM_014278]
HSPD1	Homo sapiens heat shock 60kDa protein 1 (chaperonin) (HSPD1), nuclear gene encoding mitochondrial protein, transcript variant 1, mRNA [NM_002156]
IGSF9	Homo sapiens immunoglobulin superfamily, member 9 (IGSF9), mRNA [NM_020789]
INPP5D	Homo sapiens inositol polyphosphate-5-phosphatase, 145kDa (INPP5D), transcript variant 1, mRNA [NM_001017915]
ITPR1	Homo sapiens inositol 1,4,5-triphosphate receptor, type 1 (ITPR1), mRNA [NM_002222]
KLF15	Homo sapiens Kruppel-like factor 15 (KLF15), mRNA [NM_014079]
KLHL23	Homo sapiens kelch-like 23 (Drosophila) (KLHL23), mRNA [NM_144711]
KLK3	Homo sapiens mRNA for putative preproPSA-RP2 (KLK3 gene), transcript 2. [AJ310938]
LOC153346	Homo sapiens cDNA FLJ14284 fis, clone PLACE1005898. [AK024346]
LOC401010	Homo sapiens hypothetical LOC401010 (LOC401010) on chromosome 2 [NR_002826]
LOC442240	Homo sapiens mRNA; cDNA DKFZp781A1422 (from clone DKFZp781A1422). [CR627448]
LOC729915	PREDICTED: Homo sapiens similar to Nuclear envelope pore membrane protein POM 121 (Pore membrane protein of 121 kDa) (P145) (LOC729915), mRNA [XR_015700]
LRRC61	Homo sapiens leucine rich repeat containing 61 (LRRC61), mRNA [NM_023942]
LRRC8B	Homo sapiens leucine rich repeat containing 8 family, member B (LRRC8B), mRNA [NM_015350]
MAB21L2	Homo sapiens mab-21-like 2 (C. elegans) (MAB21L2), mRNA [NM_006439]
MGC2408	Homo sapiens hypothetical protein MGC2408 (MGC2408), mRNA [NM_032331]
MIG7	Homo sapiens MIG7 (MIG7) mRNA, complete cds. [DQ080207]
MYBBP1A	Homo sapiens MYB binding protein (P160) 1a (MYBBP1A), mRNA [NM_014520]
NEFH	Homo sapiens neurofilament, heavy polypeptide 200kDa (NEFH), mRNA [NM_021076]
NETO2	Homo sapiens neuropilin (NRP) and tolloid (TLL)-like 2 (NETO2), mRNA [NM_018092]
NP1247838	GB|AL162389.21|CAH73163.1 ribosomal protein L36a pseudogene 6 [Homo sapiens] [NP1247838]
NPM3	Homo sapiens nucleophosmin/nucleoplasmin, 3 (NPM3), mRNA [NM_006993]
NPW	Neuropeptide W precursor (Preproprotein L8) (hPPL8) [Contains: Neuropeptide W-23 (NPW23) (hL8); Neuropeptide W-30 (NPW30) (hL8C)]. [Source:Uniprot/SWISSPROT;Acc:Q8N729] [ENST00000329610]
NR0B1	Homo sapiens nuclear receptor subfamily 0, group B, member 1 (NR0B1), mRNA [NM_000475]
ORC2L	Homo sapiens origin recognition complex, subunit 2-like (yeast) (ORC2L), mRNA [NM_006190]
P2RX5	Homo sapiens purinergic receptor P2X, ligand-gated ion channel, 5 (P2RX5), transcript variant 1, mRNA [NM_002561]
PEO1	Homo sapiens progressive external ophthalmoplegia 1 (PEO1), mRNA [NM_021830]
PRPF19	Homo sapiens PRP19/PSO4 pre-mRNA processing factor 19 homolog (S. cerevisiae) (PRPF19), mRNA [NM_014502]
PRR7	Homo sapiens proline rich 7 (synaptic) (PRR7), mRNA [NM_030567]
RASGEF1C	Homo sapiens RasGEF domain family, member 1C (RASGEF1C), mRNA [NM_175062]
RCC1	Homo sapiens regulator of chromosome condensation 1 (RCC1), transcript variant 3, mRNA [NM_001269]
RGS16	Homo sapiens regulator of G-protein signalling 16 (RGS16), mRNA [NM_002928]
RHBDF2	Homo sapiens rhomboid 5 homolog 2 (Drosophila) (RHBDF2), transcript variant 1, mRNA [NM_024599]
RRP9	Homo sapiens RRP9, small subunit (SSU) processome component, homolog (yeast) (RRP9), mRNA [NM_004704]
SCARB1	Homo sapiens scavenger receptor class B, member 1 (SCARB1), transcript variant 1, mRNA [NM_005505]
SLC19A1	Homo sapiens solute carrier family 19 (folate transporter), member 1 (SLC19A1), mRNA [NM_194255]
SLC19A3	Homo sapiens solute carrier family 19, member 3 (SLC19A3), mRNA [NM_025243]
SLC5A6	Homo sapiens solute carrier family 5 (sodium-dependent vitamin transporter), member 6 (SLC5A6), mRNA [NM_021095]
SLC6A15	Homo sapiens solute carrier family 6, member 15 (SLC6A15), transcript variant 1, mRNA [NM_182767]
ST6GAL1	Homo sapiens ST6 beta-galactosamide alpha-2,6-sialyltranferase 1 (ST6GAL1), transcript variant 1, mRNA [NM_173216]
TAF4B	Transcription initiation factor TFIID subunit 4B (Transcription initiation factor TFIID 105 kDa subunit) (TAFII-105) (TAFII105). [Source:Uniprot/SWISSPROT;Acc:Q92750] [ENST00000269142]
tcag7.1239	PREDICTED: Homo sapiens similar to Huntingtin interacting protein K (LOC643438), misc RNA [XR_015268]
THC2498220	Q30VC0_DESDG (Q30VC0) Flagellar biosynthetic protein FliP, partial (8%) [THC2498220]
THC2537217	
THC2654127	XKR4_MOUSE (Q5GH67) XK-related protein 4, partial (3%) [THC2654127]
THC2694828	Q3SDF2_PARTE (Q3SDF2) EPI21 protein, partial (5%) [THC2694828]
THC2730631	ARL9_HUMAN (Q6T311) ADP-ribosylation factor-like protein 9, partial (39%) [THC2730631]
TMEM97	Homo sapiens transmembrane protein 97 (TMEM97), mRNA [NM_014573]
TRIM14	Homo sapiens tripartite motif-containing 14 (TRIM14), transcript variant 1, mRNA [NM_014788]
WDR4	Homo sapiens WD repeat domain 4 (WDR4), transcript variant 2, mRNA [NM_033661]
ZNF342	Homo sapiens zinc finger protein 342 (ZNF342), mRNA [NM_145288]
ZNF485	Homo sapiens zinc finger protein 485 (ZNF485), mRNA [NM_145312]

Group AC

GeneSymbol	Description
A_23_P108534	
A_24_P315885	

A_24_P587993	
A_24_P678056	
A_32_P73143	
ANP32A	Homo sapiens acidic (leucine-rich) nuclear phosphoprotein 32 family, member A (ANP32A), mRNA [NM_006305]
ANP32D	Homo sapiens acidic (leucine-rich) nuclear phosphoprotein 32 family, member D (ANP32D), mRNA [NM_012404]
APH1A	Homo sapiens anterior pharynx defective 1 homolog A (C. elegans) (APH1A), transcript variant 2, mRNA [NM_016022]
BAX	Homo sapiens BCL2-associated X protein (BAX), transcript variant sigma, mRNA [NM_138765]
C10orf46	Homo sapiens chromosome 10 open reading frame 46 (C10orf46), mRNA [NM_153810]
C5orf5	Homo sapiens chromosome 5 open reading frame 5 (C5orf5), mRNA [NM_016603]
CSTF2T	Homo sapiens cleavage stimulation factor, 3' pre-RNA, subunit 2, 64kDa, tau variant (CSTF2T), mRNA [NM_015235]
CTSZ	Homo sapiens cathepsin Z (CTSZ), mRNA [NM_001336]
EPB41	Homo sapiens erythrocyte membrane protein band 4.1 (elliptocytosis 1, RH-linked) (EPB41), transcript variant 3, mRNA [NM_004437]
FAM60A	Protein FAM60A (Tera protein homolog). [Source:Uniprot/SWISSPROT;Acc:Q9NP50] [ENST00000337682]
FLJ36874	Homo sapiens FLJ36874 protein (FLJ36874), mRNA [NM_152716]
H2AFB2	Homo sapiens H2A histone family, member B2 (H2AFB2), mRNA [NM_001017991]
HIRA	Homo sapiens HIR histone cell cycle regulation defective homolog A (S. cerevisiae) (HIRA), mRNA [NM_003325]
HNRPA0	Homo sapiens heterogeneous nuclear ribonucleoprotein A0 (HNRPA0), mRNA [NM_006805]
HPDL	Homo sapiens 4-hydroxyphenylpyruvate dioxygenase-like (HPDL), mRNA [NM_032756]
IPO7	Homo sapiens importin 7 (IPO7), mRNA [NM_006391]
KIFC1	Homo sapiens kinesin family member C1 (KIFC1), mRNA [NM_002263]
LIMK1	Homo sapiens LIM domain kinase 1 (LIMK1), mRNA [NM_002314]
LMNB1	Homo sapiens lamin B1 (LMNB1), mRNA [NM_005573]
LOC128192	PREDICTED: Homo sapiens similar to peptidylprolyl isomerase A isoform 1 (LOC128192), mRNA [XM_060887]
LOC284242	Homo sapiens, clone IMAGE:5745916, mRNA. [BC035844]
LOC728347	AGENCOURT_8185067 NIH_MGC_102 Homo sapiens cDNA clone IMAGE:6257517 5', mRNA sequence [BQ674642]
LOC730589	PREDICTED: Homo sapiens hypothetical protein LOC730589 (LOC730589), mRNA [XM_001126447]
MAGOH	Homo sapiens mago-nashi homolog, proliferation-associated (Drosophila) (MAGOH), mRNA [NM_002370]
MEX3A	Homo sapiens cDNA FLJ43493 fis, clone OCBBF3009279. [AK125482]
MORN1	Homo sapiens MORN repeat containing 1 (MORN1), mRNA [NM_024848]
MYADM	Homo sapiens myeloid-associated differentiation marker (MYADM), transcript variant 2, mRNA [NM_138373]
PCDHB9	Homo sapiens protocadherin beta 9 (PCDHB9), mRNA [NM_019119]
PPP3R1	Homo sapiens protein phosphatase 3 (formerly 2B), regulatory subunit B, alpha isoform (PPP3R1), mRNA [NM_000945]
RNF121	Homo sapiens ring finger protein 121 (RNF121), transcript variant 1, mRNA [NM_018320]
RSRC2	Homo sapiens arginine/serine-rich coiled-coil 2 (RSRC2), transcript variant 2, mRNA [NM_198261]
SAA2	Homo sapiens serum amyloid A2 (SAA2), mRNA [NM_030754]
SLC39A7	Homo sapiens solute carrier family 39 (zinc transporter), member 7 (SLC39A7), transcript variant 1, mRNA [NM_006979]
SLC6A15	Homo sapiens solute carrier family 6, member 15 (SLC6A15), transcript variant 1, mRNA [NM_182767]
SMOC1	Homo sapiens SPARC related modular calcium binding 1 (SMOC1), transcript variant 2, mRNA [NM_022137]
TAF5L	Homo sapiens TAF5-like RNA polymerase II, p300/CBP-associated factor (PCAF)-associated factor, 65kDa (TAF5L), transcript variant 1, mRNA [NM_014409]
THC2635386	
TMED9	Homo sapiens transmembrane emp24 protein transport domain containing 9 (TMED9), mRNA [NM_017510]
UBE2E1	Homo sapiens ubiquitin-conjugating enzyme E2E 1 (UBC4/5 homolog, yeast) (UBE2E1), transcript variant 1, mRNA [NM_003341]
USP21	Homo sapiens ubiquitin specific peptidase 21 (USP21), transcript variant 1, mRNA [NM_012475]
XPR1	Homo sapiens xenotropic and polytropic retrovirus receptor (XPR1), mRNA [NM_004736]

Group C

GeneSymbol	Description
A_24_P935852	
BCL11A	Homo sapiens B-cell CLL/lymphoma 11A (zinc finger protein) (BCL11A), transcript variant 1, mRNA [NM_022893]
EYA2	Homo sapiens eyes absent homolog 2 (Drosophila) (EYA2), transcript variant 2, mRNA [NM_172113]
LOC647968	PREDICTED: Homo sapiens similar to M-phase phosphoprotein 10 (LOC647968), mRNA [XR_018268]
MAPT	Homo sapiens microtubule-associated protein tau (MAPT), transcript variant 1, mRNA [NM_016835]
MED18	Homo sapiens mediator of RNA polymerase II transcription, subunit 18 homolog (S. cerevisiae) (MED18), mRNA [NM_017638]
RFPL1S	Homo sapiens ret finger protein-like 1 antisense (RFPL1S) on chromosome 22 [NR_002727]
RNF145	Homo sapiens hypothetical protein FLJ31951 (FLJ31951), mRNA [NM_144726]
THC2520867	ALU1_HUMAN (P39188) Alu subfamily J sequence contamination warning entry, partial (6%) [THC2520867]
TTBK2	Homo sapiens tau tubulin kinase 2 (TTBK2), mRNA [NM_173500]

Group B

GeneSymbol	Description
A_24_P877411	
A_24_P926115	
A_32_P51714	
AA081809	AA081809 zn26e08.r1 Stratagene neuroepithelium NT2RAMI 937234 Homo sapiens cDNA clone IMAGE:548582 5', mRNA sequence [AA081809]
ABI3	Homo sapiens ABI gene family, member 3 (ABI3), mRNA [NM_016428]
AF086335	Homo sapiens full length insert cDNA clone ZD55G10. [AF086335]
AF161340	Homo sapiens HSPC077 mRNA, partial cds. [AF161340]
AF234262	Homo sapiens IL-1beta-regulated neutrophil survival protein mRNA, complete cds. [AF234262]
AK000313	Homo sapiens cDNA FLJ20306 fis, clone HEP06881. [AK000313]
AK024092	Homo sapiens cDNA FLJ14030 fis, clone HEMBA1004086. [AK024092]
AK090463	Homo sapiens mRNA for FLJ00384 protein. [AK090463]
AK124698	Homo sapiens cDNA FLJ42708 fis, clone BRAMY3007311. [AK124698]
ALOX15B	Homo sapiens arachidonate 15-lipoxygenase, type B (ALOX15B), transcript variant d, mRNA [NM_001141]
ANAPC1	Homo sapiens anaphase promoting complex subunit 1 (ANAPC1), mRNA [NM_022662]
ATF3	Homo sapiens activating transcription factor 3 (ATF3), transcript variant 2, mRNA [NM_004024]
BC020341	Homo sapiens cDNA clone IMAGE:4177218. [BC020341]
BC031342	Homo sapiens, clone IMAGE:5019307, mRNA. [BC031342]
BC042947	Homo sapiens cDNA clone IMAGE:4797785. [BC042947]
CCL4	Homo sapiens chemokine (C-C motif) ligand 4 (CCL4), transcript variant 1, mRNA [NM_002984]
CD274	Homo sapiens CD274 molecule (CD274), mRNA [NM_014143]
CHD9	Homo sapiens chromodomain helicase DNA binding protein 9 (CHD9), mRNA [NM_025134]
CISH	Homo sapiens cytokine inducible SH2-containing protein (CISH), mRNA [NM_145071]
DENND4A	Homo sapiens DENN/MADD domain containing 4A (DENND4A), mRNA [NM_005848]
DOK3	Homo sapiens docking protein 3 (DOK3), mRNA [NM_024872]
ECH1	Homo sapiens, clone IMAGE:3858114, mRNA. [BC014786]
EDG5	Homo sapiens endothelial differentiation, sphingolipid G-protein-coupled receptor, 5 (EDG5), mRNA [NM_004230]
ENST00000291567	Glucose-6-phosphate 1-dehydrogenase (EC 1.1.1.49) (G6PD). [Source:Uniprot/SWISSPROT;Acc:P11413] [ENST00000291567]
ENST00000299419	Q7D724_MYCTU (Q7D724) PE_PGRS family protein (PE-PGRS FAMILY PROTEIN), partial (3%) [THC2672762]
FAIM2	Homo sapiens Fas apoptotic inhibitory molecule 2 (FAIM2), mRNA [NM_012306]
LCE1F	Homo sapiens late cornified envelope 1F (LCE1F), mRNA [NM_178354]
LOC338328	Homo sapiens high density lipoprotein-binding protein (LOC338328), mRNA [NM_178172]
LOC390614	PREDICTED: Homo sapiens hypothetical LOC390614 (LOC390614), mRNA [XR_018320]
LOC642006	PREDICTED: Homo sapiens similar to Beta-glucuronidase precursor (Beta-G1) (LOC642006), mRNA [XR_018069]
MGC23985	Homo sapiens similar to AVLV472 (MGC23985), mRNA [NM_206966]
NPNT	Homo sapiens nephronectin (NPNT), mRNA [NM_001033047]
NUDT22	Homo sapiens cDNA FLJ34477 fis, clone HLUNG2003833. [AK091796]
OLIG1	Homo sapiens oligodendrocyte transcription factor 1 (OLIG1), mRNA [NM_138983]
PCDH7	Homo sapiens protocadherin 7 (PCDH7), transcript variant c, mRNA [NM_032457]
PGS1	Homo sapiens phosphatidylglycerophosphate synthase 1 (PGS1), mRNA [NM_024419]
RALGDS	Homo sapiens ral guanine nucleotide dissociation stimulator (RALGDS), transcript variant 1, mRNA [NM_006266]
RGPD1	Homo sapiens RANBP2-like and GRIP domain containing 1 (RGPD1), mRNA [NM_001024457]
RHOF	Homo sapiens ras homolog gene family, member F (in filopodia) (RHOF), mRNA [NM_019034]
RREB1	Homo sapiens ras responsive element binding protein 1 (RREB1), transcript variant 2, mRNA [NM_002955]
SPTBN2	Homo sapiens spectrin, beta, non-erythrocytic 2 (SPTBN2), mRNA [NM_006946]
TBC1D22B	Homo sapiens TBC1 domain family, member 22B (TBC1D22B), mRNA [NM_017772]
TEKT5	Homo sapiens tektin 5 (TEKT5), mRNA [NM_144674]
THC2562932	Q52M62_HUMAN (Q52M62) LOC285908 protein, partial (28%) [THC2562932]
THC2723431	Q93V73_MAIZE (Q93V73) Globulin 1 (Fragment), partial (7%) [THC2723431]
THC2752681	
TRIM50	Homo sapiens tripartite motif-containing 50 (TRIM50), mRNA [NM_178125]
ZNF75	Homo sapiens zinc finger protein 75 (D8C6) (ZNF75), mRNA [NM_007131]
ZRANB3	Homo sapiens zinc finger, RAN-binding domain containing 3 (ZRANB3), mRNA [NM_032143]

Group BD

GeneSymbol	Description
A_23_P412927	
A_23_P46070	
A_24_P401663	
A_24_P689119	

A_24_P752279	
A_24_P753638	
A_24_P828125	
A_24_P834210	
A_32_P11425	
A_32_P37943	
ACBD4	Homo sapiens acyl-Coenzyme A binding domain containing 4 (ACBD4), mRNA [NM_024722]
AK024371	Homo sapiens cDNA FLJ14309 fis, clone PLACE3000221. [AK024371]
ANKRD42	Homo sapiens ankyrin repeat domain 42 (ANKRD42), mRNA [NM_182603]
AP2B1	Homo sapiens adaptor-related protein complex 2, beta 1 subunit (AP2B1), transcript variant 2, mRNA [NM_001282]
BC034930	Homo sapiens, clone IMAGE:4579561, mRNA. [BC034930]
BC044608	Homo sapiens cDNA clone IMAGE:4827340. [BC044608]
BC070091	Homo sapiens caspase recruitment domain family, member 9, mRNA (cDNA clone MGC:87491 IMAGE:30343821), complete cds. [BC070091]
BE719776	BE719776 RC3-HT0865-260700-011-b02 HT0865 Homo sapiens cDNA, mRNA sequence [BE719776]
C19orf31	Homo sapiens chromosome 19 open reading frame 31 (C19orf31), mRNA [NM_001014373]
C7	Homo sapiens complement component 7 (C7), mRNA [NM_000587]
CEBPA	Homo sapiens CCAAT/enhancer binding protein (C/EBP), alpha (CEBPA), mRNA [NM_004364]
CHRNA4	H.sapiens mRNA for neuronal acetylcholine receptor alpha-4 subunit, exon 1. [X89741]
COX6B2	Homo sapiens cytochrome c oxidase subunit VIb polypeptide 2 (testis) (COX6B2), mRNA [NM_144613]
CR594528	full-length cDNA clone CS0DM002YC17 of Fetal liver of Homo sapiens (human) [CR594528]
CYP4F2	Homo sapiens cytochrome P450, family 4, subfamily F, polypeptide 2 (CYP4F2), mRNA [NM_001082]
DKFZP434I0714	PREDICTED: Homo sapiens hypothetical protein DKFZP434I0714 (DKFZP434I0714), mRNA [XM_929673]
DOCK3	Homo sapiens dedicator of cytokinesis 3 (DOCK3), mRNA [NM_004947]
ECSM2	Homo sapiens endothelial cell-specific molecule 2 (ECSM2), mRNA [NM_001077693]
EDA2R	Homo sapiens ectodysplasin A2 receptor (EDA2R), mRNA [NM_021783]
ENST00000302096	bA299N6.3 (LOC198437), mRNA [Source:RefSeq_dna;Acc:NM_001007125] [ENST00000302096]
ENST00000320010	Putative uncharacterized protein C11orf37. [Source:Uniprot/SWISSPROT;Acc:Q96N53] [ENST00000320010]
ENST00000378644	Homo sapiens, clone IMAGE:5728979, mRNA. [BC035731]
EPPK1	Homo sapiens epiplakin 1 (EPPK1), mRNA [NM_031308]
FLJ35934	Homo sapiens cDNA FLJ35934 fis, clone TESTI2011315. [AK093253]
FMO5	Homo sapiens flavin containing monooxygenase 5 (FMO5), mRNA [NM_001461]
FRMD4A	Homo sapiens FERM domain containing 4A (FRMD4A), mRNA [NM_018027]
GEFT	Homo sapiens RAC/CDC42 exchange factor (GEFT), transcript variant 2, mRNA [NM_133483]
HSD17B1	Homo sapiens, clone IMAGE:5443970, mRNA, partial cds. [BC033110]
IQSEC1	Homo sapiens IQ motif and Sec7 domain 1 (IQSEC1), mRNA [NM_014869]
KISS1R	Homo sapiens KISS1 receptor (KISS1R), mRNA [NM_032551]
KRT18P40	PREDICTED: Homo sapiens similar to Keratin, type I cytoskeletal 18 (Cytokeratin-18) (CK-18) (Keratin-18) (K18) (LOC390904), mRNA [XR_017288]
LOC145694	Homo sapiens cDNA FLJ32231 fis, clone PLACE6004491. [AK056793]
LOC339344	Homo sapiens hypothetical protein LOC339344 (LOC339344), mRNA [NM_001012643]
LOC392617	PREDICTED: Homo sapiens similar to slit homolog 1 (LOC392617), mRNA [XM_001132524]
LOC643594	PREDICTED: Homo sapiens similar to CG13731-PA (LOC643594), mRNA [XM_926898]
LOC646643	Putative uncharacterized serine/threonine-protein kinase SgK069 (EC 2.7.11.1) (Sugen kinase 69). [Source:Uniprot/SWISSPROT;Acc:P0C263] [ENST00000344158]
LOC646960	PREDICTED: Homo sapiens similar to transmembrane protease, serine 9 (LOC646960), mRNA [XM_929928]
LOC650392	Homo sapiens hypothetical protein LOC650392, mRNA (cDNA clone IMAGE:5242623), partial cds. [BC028099]
LOC730498	PREDICTED: Homo sapiens similar to zinc finger protein 561 (LOC730498), mRNA [XR_015158]
LOC731997	PREDICTED: Homo sapiens hypothetical protein LOC731997 (LOC731997), mRNA [XM_001131542]
LRP3	Homo sapiens low density lipoprotein receptor-related protein 3 (LRP3), mRNA [NM_002333]
MGC21874	Homo sapiens cDNA FLJ45019 fis, clone BRAWH3015825. [AK126966]
MGC34800	Homo sapiens hypothetical protein MGC34800, mRNA (cDNA clone MGC:34800 IMAGE:5167909), complete cds. [BC029861]
MOP-1	Homo sapiens mRNA for MOP-1, complete cds. [AB014771]
MYCN	Homo sapiens v-myc myelocytomatosis viral related oncogene, neuroblastoma derived (avian) (MYCN), mRNA [NM_005378]
NEUROG1	Homo sapiens neurogenin 1 (NEUROG1), mRNA [NM_006161]
NEUROG3	Homo sapiens neurogenin 3 (NEUROG3), mRNA [NM_020999]
NKD2	Homo sapiens naked cuticle homolog 2 (Drosophila) (NKD2), mRNA [NM_033120]
NP511100	GB|AB065467.1|BAC05726.1 seven transmembrane helix receptor [Homo sapiens] [NP511100]
PAX7	Homo sapiens paired box gene 7 (PAX7), transcript variant 2, mRNA [NM_013945]
PCSK1N	Homo sapiens proprotein convertase subtilisin/kexin type 1 inhibitor (PCSK1N), mRNA [NM_013271]
PIP5K1C	Homo sapiens phosphatidylinositol-4-phosphate 5-kinase, type I, gamma (PIP5K1C), mRNA [NM_012398]
PRLH	Homo sapiens prolactin releasing hormone (PRLH), mRNA [NM_015893]
PSORS1C2	Homo sapiens psoriasis susceptibility 1 candidate 2 (PSORS1C2), mRNA [NM_014069]
RHBDL1	Homo sapiens rhomboid, veinlet-like 1 (Drosophila) (RHBDL1), mRNA [NM_003961]
S72478	BCR...ABL {b3/a3 junction, translocation breakpoint} [human, Japanese CML patient 1 and ALL patient 2, peripheral blood, mononuclear cells, mRNA Mutant, 3 genes, 140 nt]. [S72478]
SAMD10	Homo sapiens sterile alpha motif domain containing 10 (SAMD10), mRNA [NM_080621]
SOX8	Homo sapiens SRY (sex determining region Y)-box 8 (SOX8), mRNA [NM_014587]
SP5	Homo sapiens Sp5 transcription factor (SP5), mRNA [NM_001003845]
SPSB4	Homo sapiens splA/ryanodine receptor domain and SOCS box containing 4 (SPSB4), mRNA [NM_080862]
THC2545702	
THC2585656	Q6NVT1_XENTR (Q6NVT1) RNA binding motif protein 25, partial (7%) [THC2585656]
THC2636500	
THC2669063	AI500335 tm95e03.x1 NCI_CGAP_Brn25 Homo sapiens cDNA clone IMAGE:2165884 3', mRNA sequence [AI500335]
THC2678411	Q34Z38_9GAMM (Q34Z38) Outer membrane efflux protein precursor, partial (5%) [THC2678411]
THC2689192	Q7XC69_ORYSA (Q7XC69) Expressed protein, partial (6%) [THC2689192]
THC2719256	BE147120 PM2-HT0224-221099-001-b10 HT0224 Homo sapiens cDNA, mRNA sequence [BE147120]
TNXB	Homo sapiens tenascin XB (TNXB), transcript variant XB, mRNA [NM_019105]
TRIM35	Homo sapiens tripartite motif-containing 35 (TRIM35), transcript variant 2, mRNA [NM_171982]
TSPAN10	Homo sapiens tetraspanin 10 (TSPAN10), mRNA [NM_031945]
U01925	Human BTK region clone 2f10-rpi mRNA. [U01925]
VASH2	Homo sapiens vasohibin 2 (VASH2), mRNA [NM_024749]
Y10152	H.sapiens mRNA for CRF2 receptor, beta isoform, aberrantly spliced, (94bp deletion). [Y10152]
ZNF687	Homo sapiens zinc finger protein 687 (ZNF687), mRNA [NM_020832]
ZSCAN10	Homo sapiens zinc finger and SCAN domain containing 10 (ZSCAN10), mRNA [NM_032805]

Group_D	
GeneSymbol	Description
A_24_P153002	
A_24_P247169	
A_24_P384469	
A_24_P461664	
A_24_P745960	
A_24_P76288	
A_24_P7785	
A_32_P101073	
A_32_P105865	
A_32_P139021	
A_32_P62137	
A_32_P77759	
A_32_P90178	
ALDOA	Homo sapiens aldolase A, fructose-bisphosphate (ALDOA), transcript variant 2, mRNA [NM_184041]
ANKDD1A	Homo sapiens cDNA FLJ25870 fis, clone CBR02141. [AK098736]
AW167080	AW167080 xg70g01.x1 NCI_CGAP_Ut4 Homo sapiens cDNA clone IMAGE:2633712 3', mRNA sequence [AW167080]
BC028232	Homo sapiens, clone IMAGE:5221276, mRNA, partial cds. [BC028232]
BC036435	Homo sapiens cDNA clone IMAGE:4816083, partial cds. [BC036435]
BHLHB4	Homo sapiens basic helix-loop-helix domain containing, class B, 4 (BHLHB4), mRNA [NM_080606]
BM547196	BM547196 AGENCOURT_6499364 NIH_MGC_124 Homo sapiens cDNA clone IMAGE:5730270 5', mRNA sequence [BM547196]
C16orf3	Homo sapiens chromosome 16 open reading frame 3 (C16orf3), mRNA [NM_001214]
C21orf58	Homo sapiens chromosome 21 open reading frame 58 (C21orf58), transcript variant 2, mRNA [NM_199071]
CACNA1E	Homo sapiens calcium channel, voltage-dependent, R type, alpha 1E subunit (CACNA1E), mRNA [NM_000721]
CCDC108	Homo sapiens coiled-coil domain containing 108 (CCDC108), transcript variant 1, mRNA [NM_194302]
CLEC4M	Homo sapiens C-type lectin domain family 4, member M (CLEC4M), transcript variant 4, mRNA [NM_214677]
CMIP	Homo sapiens c-Maf-inducing protein (CMIP), transcript variant C-mip, mRNA [NM_198390]
CPXM1	Homo sapiens carboxypeptidase X (M14 family), member 1 (CPXM1), mRNA [NM_019609]
CYB561D1	Homo sapiens cytochrome b-561 domain containing 1 (CYB561D1), mRNA [NM_182580]
DDX6	Homo sapiens DEAD (Asp-Glu-Ala-Asp) box polypeptide 6 (DDX6), mRNA [NM_004397]
DYRK1A	Homo sapiens mRNA for MNB/DYRK protein kinase, partial cds, alternatively spliced transcript MNB31. [AB015282]
ENST00000324745	Homo sapiens mRNA for FLJ00388 protein. [AK090467]
ENST00000359589	
FLJ35390	Homo sapiens hypothetical protein FLJ35390, mRNA (cDNA clone IMAGE:4328569), with apparent retained intron. [BC024303]
FOXRED2	Homo sapiens FAD-dependent oxidoreductase domain containing 2 (FOXRED2), mRNA [NM_024955]

GH2	Homo sapiens growth hormone 2 (GH2), transcript variant 3, mRNA [NM_022558]
IFITM5	Homo sapiens interferon induced transmembrane protein 5 (IFITM5), mRNA [NM_001025295]
KIAA1545	Homo sapiens XTP9 (XTP9) mRNA, complete cds. [AF490258]
KLK3	Homo sapiens prostate-specific antigen variant 2 mRNA, complete cds, alternatively spliced. [AF335478]
LCE1D	Homo sapiens late cornified envelope 1D (LCE1D), mRNA [NM_178352]
LOC146325	Homo sapiens similar to hypothetical protein FLJ13841 (LOC146325), mRNA [NM_145270]
LOC649294	Homo sapiens cDNA FLJ33940 fis, clone CTONG2018069. [AK091259]
LOC728449	annexin A8 [Source:RefSeq_peptide;Acc:NP_001621] [ENST00000335083]
LOC728864	PREDICTED: Homo sapiens similar to Mucin-2 precursor (Intestinal mucin 2) (LOC728864), mRNA [XM_001128654]
LOC729956	PREDICTED: Homo sapiens hypothetical protein LOC729956 (LOC729956), mRNA [XM_001131873]
LOC90113	PREDICTED: Homo sapiens hypothetical protein BC009862 (LOC90113), mRNA [XM_291077]
LYPD3	Homo sapiens LY6/PLAUR domain containing 3 (LYPD3), mRNA [NM_014400]
MCOLN2	Homo sapiens mucolipin 2 (MCOLN2), mRNA [NM_153259]
MGC13057	Homo sapiens hypothetical protein MGC13057 (MGC13057), transcript variant 4, mRNA [NM_032321]
MLXIPL	Homo sapiens MLX interacting protein-like (MLXIPL), transcript variant 4, mRNA [NM_032954]
NKX1-2	PREDICTED: Homo sapiens NK1 transcription factor related, locus 2 (Drosophila) (NKX1-2), mRNA [XM_372331]
NP111687	GB|L33988.1|AAA74365.1 ORF [NP111687]
NRSN2	Homo sapiens neurensin 2 (NRSN2), mRNA [NM_024958]
PCSK1N	Homo sapiens proprotein convertase subtilisin/kexin type 1 inhibitor (PCSK1N), mRNA [NM_013271]
POU3F3	Homo sapiens POU domain, class 3, transcription factor 3 (POU3F3), mRNA [NM_006236]
PRIC285	Homo sapiens peroxisomal proliferator-activated receptor A interacting complex 285 (PRIC285), transcript variant 2, mRNA [NM_033405]
RFX3	Transcription factor RFX3. [Source:Uniprot/SWISSPROT;Acc:P48380] [ENST00000382004]
SF3A2	Homo sapiens splicing factor 3a, subunit 2, 66kDa (SF3A2), mRNA [NM_007165]
SPPL2B	Homo sapiens signal peptide peptidase-like 2B (SPPL2B), transcript variant 3, mRNA [NM_001077238]
SYNGR4	Homo sapiens synaptogyrin 4 (SYNGR4), mRNA [NM_012451]
TANC2	Homo sapiens mRNA for putative ankyrin-repeat containing protein (ORF1). [AJ278120]
THC2503530	AA360388 EST69518 T-cell lymphoma Homo sapiens cDNA 5' end similar to EST containing Alu repeat, mRNA sequence [AA360388]
THC2529614	Q3VHI9 9SPHN (Q3VHI9) Manganese and iron superoxide dismutase precursor, partial (8%) [THC2529614]
THC2532927	Q7Z637 HUMAN (Q7Z637) PTPN18 protein, partial (13%) [THC2532927]
THC2658813	
THC2678806	HESX1 HUMAN (Q9UBX0) Homeobox expressed in ES cells 1 (Homeobox protein ANF) (hAnf), partial (70%) [THC2678806]
THC2689579	BPAP BOVIN (P84291) Pregnancy-associated protein bPAP (Fragments), partial (10%) [THC2689579]
THC2717131	Q7NI46 GLOVI (Q7NI46) Cytochrome c550, partial (8%) [THC2717131]
THC2752750	
TLE6	Homo sapiens transducin-like enhancer of split 6 (E(spl) homolog, Drosophila) (TLE6), mRNA [NM_024760]
UCN2	Homo sapiens urocortin 2 (UCN2), mRNA [NM_033199]

Supplementary Table 2 Primers used for cloning

Genes	Sequences
Hu-L-Myc	CAC CAT GGA CTA CGA CTC GTA CCA GCA CT
	TTA GTA GCC AGT GAG GTA TGC AAT TC
Hu-N-Myc	CAC CAT GCC GAG CTG CTC CAC GTC CAC C
	GAA AAT TGA ACA CGC TCG GAC TTG CTA G

Supplementary Table 3 Primers used for deletion mutants

Genes	Sequences
Hu-c-Myc-dN1 (dN1)	CAC CAT GCT CGA CTA CGA CTC GGT GCA GCC
	TTA CGC ACA AGA GTT CCG TAG CTG TTC AAG
Hu-c-Myc-dN2 (dN2)	CAC CAT GCC CCC GGC GCC CAG CGA GGA TAT
	TTA CGC ACA AGA GTT CCG TAG CTG TTC AAG

Supplementary Table 4 Primers used for site-directed mutagenesis

Genes	Sequences
Ms-c-Myc-W136E	CAG GAC TGT ATG GAG AGC GGT TTC TC
	GAG AAA CCG CTC TCC ATA CAG TCC TG
Ms-c-Myc-V394D	GCC CCC AAG GTA GAT ATC CTC AAA AAA G
	CTT TTT TGA GGA TAT CTA CCT TGG GGG C
Ms-c-Myc-L420P	GAA AAG GAC TTA CCG AGG AAA CGA CG
	CGT CGT TTC CTC GGT AAG TCC TTT TC
Ms-L-Myc-L351P	AGA AAA GGC AGC CCC GGT GTC GGC A
	TGC CGA CAC CGG GGC TGC CTT TTC T

Supplementary Table 5 Primers used for RT-PCR

Genes	Sequences
Ms-L-Myc Total	CAC TGA GGA CGT GAC CAA GA
	TTA GTA GCC ACT GAG GTA CGC GAT TCT CTT
Ms-L-Myc Tg	CAC TGA GGA CGT GAC CAA GA
	GAC ATG GCC TGC CCG GTT ATT ATT
Hu-L-Myc Total	GTG AGT CCC CCA CCT GTA GA
	TTA GTA GCC AGT GAG GTA TGC AAT TC
Hu-L-Myc Tg	GTG AGT CCC CCA CCT GTA GA
	GAC ATG GCC TGC CCG GTT ATT ATT